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EXAMINER

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

(PAPER 27)

☒ Responsive to communication(s) filed on 1/17/97 (PAPER 24), 3/19/97 (PAPER 26) & 3/19/97.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 60-67 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 60-67 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 27
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1815**.

Applicant's arguments filed March 19, 1997 have been fully considered but they are not deemed to be persuasive.

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on March 19, 1997 has been entered.

Claims 60-67 are rejected under 35 U.S.C. § 112, first paragraph, as the specification fails to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The examiner will first discuss the Young Declaration (Attachment A), then Applicant's citation of precedent and the specification in relation to the *Forman* factors and finally Applicant's response to specific points made in the preceding Office Action.

YOUNG DECLARATION (ATTACHMENT A)

The Young Declaration (Attachment A) under 37 C.F.R. § 1.132 filed March 19, 1997 is insufficient to overcome the rejection of claims 60-66 based upon lack of an enabling specification as set forth in the last Office action.

In paragraph 4 of the declaration Young asserts that the term "synthetic

peptide" meant a peptide prepared by chemical synthesis. In support of this assertion Young points to 21 journal articles published prior to the filing date of SN 06/667501 (October 31, 1984). It would appear to be accurate that one of skill in the art would interpret the term "synthetic peptide" to mean one synthesized by solid-phase techniques, such as that of Merrifield. It would also appear that one of skill in the art would have recognized that synthetic peptides were of limited size and based on the art cited by Young no larger than 40 amino acids.

In paragraph 6 Young asserts that [t]he prior art was capable of making a clear distinction between a synthetic peptide (i.e. one synthesized by chemical means) and a peptide fragment generated by some other means. Exactly what this ability to make a clear distinction means is left unexplained by Young. For example, it is unclear that an antibody which recognizes a particular epitope makes any such clear distinction.

In paragraph 7 Young describes the various size synthetic peptides which had been made in the prior art before October 31, 1984. He notes that a plurality of teachings utilize peptides of 15-24 amino acids and that peptides of up to 40 amino acids have been employed in certain instances.

In paragraph 8 Young asserts that immunoassays employing synthetic peptides were known. To the extent that immunoassays designed to measure the binding of native protein or synthetic peptide were developed Young's assessment is accurate. With respect to diagnostic immunoassays for detecting serum antibodies directed toward retroviral proteins the cited art is ambiguous.

In paragraph 9 Young asserts that one of skill in the art reading the last sentence of the SUMMARY OF THE INVENTION at page 3 of the '501 specification which is:

> Based on the nucleotide sequences, synthetic peptides may also be prepared.

would have understood the statement to mean that such synthetic peptides would be useful in the immunoassays taught at pages 11, 14 and 15.

This assertion is not logical as it takes the above cited statement out of context. If one reads the entirety of the SUMMARY OF THE INVENTION it is clear that the intended use of the viral polypeptides or fragments is for vaccines.

Pages 11, 14 and 15 do speak to immunoassays in a general manner. It should be noted that page 11 states

> "The polypeptides which are expressed by the above DNA sequences may find use in a variety of ways. The polyeptides or immunologically active fragments thereof, may find use as diagnostic reagents, . . ."

At page 14 it is set forth

> The expression products of the env and gag genes and immunogenic fragments thereof having immunogenic sites may be used for screening antisera from patient's blood to determine whether antibodies are present which bind to hTLR antigens. A wide variety of assay techniques can be employed, involving labeled or unlabeled antigens.

These passages speak to expression products not synthetic polyeptides. Moreover, the person of ordinary skill would not have read "immunologically active fragment" as meaning synthetic peptide. Rather such "immunologically active fragments" were produced in the prior art by such techniques as limited proteolysis or chemical cleavage of polypeptide antigens.

In paragraph 10 Young asserts that using the Hopp algorithm that one of ordinary skill in the art could identify synthetic HIV antigenic peptides. However, Young does not establish that use of the Hopp algorithm was so widespread in 1984 that one of skill in the art would have been automatically

lead to apply it to the sequences presented in the '501 specification. There is no mention of either Hopp publication in the specification. Moreover, applicant has previously argued that the Geysen et al. (1984) strategy was well known in the art. As with Hopp the '501 specification is silent with regard to Geysen et al.

With respect to the teachings of Hopp (1983) the examiner cites the following:

> A suitable approach for applying this method is to synthesize the predicted antigenic determinant by the Merrifield peptide synthesis procedure, and then test the peptide for antigenic and immunogenic activity. It is prudent to synthesize more than just the six residues yielding the highest hydrophilicity average for several reasons: (1) other investigators have found that additional amino acids flanking the antigenic sequence often enhance the antigenic reactivity of a given sequence, probably by imparting a more native conformation to the sequence in question (Atassi & Saplin, 1968; Crumpton, 1974); (2) the predicted point sometimes lies immediately to one side of the natural antigenic determinant, so that several additional residues are required to ensure a good overlap of the synthetic peptide on the antigenic site (Hopp & Woods, 1981). Therefore, it is appropriate to synthesize peptides of no fewer than twelve residues, including three residues on either side of the six amino acids that yielded the highest average hydrophilicity value. (page 486, left hand column)

In paragraph 11 Young states that the most hydrophilic region of ARV-2 Env is the peptide ERDRDR. Young then states that publications by Broliden 1992, Goudsmit 1990 and Kennedy 1986 establish that this peptide comprises part of an epitope recognized by AIDS patient antisera. It is ironic that this peptide is from the intracellular region of gp41. The Broliden peptide is a 15-mer, the Goudsmit peptide is a 19-mer, which was assembled based on results of scanning the entire gp41 molecule with nonapeptides and the Kennedy peptide is an 18-mer. Broliden employed overlapping peptides, essentially a Geysen et al. strategy, Goudsmit employed a version of the Geysen et al.

strategy whereas Kennedy state that their peptide was predicted using a modified version of the Hopp protocol. Similarly, for the second and third most hydrophilic regions.

It is unclear how research publications which do not employ Hopp support Young's assertion that one of ordinary skill in the art would have applied the Hopp algorithm to select peptides for synthesis.

Paragraph 12 concerns gag peptides.

In paragraph 13 Young asserts that the HIV sequences in the '501 application enabled one of ordinary skill in the art to identify linear epitopes in HIV Env through the use of panels of synthetic peptides.

In paragraph 14 Young points to Altman, Green and Sutcliffe for support of this assertion. It is correct that Altman utilizes a panel of peptides, however, there is nothing in Altman which provides guidance as to how the peptides were selected. Green also employs a panel of peptides and specifically directs one to the amino and carboxy terminii. The basis for this appears to be that such regions are frequently recognized in the native viral proteins (see Sutcliffe). Sutcliffe employs a panel of peptides, however, the rules for selection appear to based on empirical studies of the surface antigen of Hepatitis B.

In paragraph 15 Young asserts that "those skilled in the art knew that a proportion of antibodies raised against native proteins could recognize epitopes contained on synthetic peptides derived from a protein sequence (Rothbard 1984; Leach 1983) or contained on proteolytic fragments (Lando 1982)." While the assertion is apparently correct it begs the question of how one knows from the polypeptide sequence which peptides will or will not react.

In paragraph 16 Young concludes that "those skilled in the art could have, without undue experimentation, used the sequence of ARV-2 Env provided in

the '501 application to generate synthetic peptides representing most of the HIV glycoprotein. These peptides could then have been tested using standard assays known in the art, and immunogenic regions of HIV Env identified."

But the art Young relies on is directed toward antibody recognition not to immunogenicity. Thus, the conclusion is invalid.

Moreover, even if one limits the consideration to antigenic peptides the conclusion is invalid. Young has provided an extensive, but not exhaustive, survey of the prior art. This survey clearly establishes that workers of ordinary skill in the art had successfully obtained synthetic peptides which reacted with antibodies which recognized intact proteins. However, the path by which workers obtained such peptides is not the same from one to another. There is no consistency in the manner in which the peptides are selected nor in the size employed.

If all that is necessary for enablement of synthetic peptides is an amino acid sequence then the '501 specification is enabling.

But from the sequence alone one cannot envision whether or not a particular peptide will be recognized by antibody. Therefore, the sequence alone is insufficient.

In paragraph 18 Young asserts that neither Montagnier (Science 225:63-66 (1984)) nor Schupbach et al.(Science 224:503-505 (May 1984) would have enabled one skilled in the art to prepare a synthetic HIV envelope polypeptide for use in an immunoassay without undue experimentation because:

a) no nucleotide sequence or amino acid sequence is presented.

But, Young does not establish that such information is not readily obtainable from fragments of viral envelope proteins.

b) sufficient quantities of HIV could not be obtained so that viral proteins

could be sequenced.

Again, Young offers no facts to support this assertion and his arguments in c) appear to contradict this position.

c) despite the fact that by October 31, 1984 both Gallo and Montagnier had reported cell lines producing significant levels of HIV one of ordinary skill in the art would not have been able to duplicate their results nor obtain their cell lines. In addition, Gallo and Montagnier were the leaders in the field and therefore not of ordinary skill.

There is no evidence to suggest that being a leader in the field results from more than ordinary skill. Young may be correct that the precise origin of the Gallo cell line is unclear, although Young does not indicate which cell line he is concerned about. Young may also be correct that cell lines identical to Montagnier might not be obtainable but it begs the question of whether or not functionally equivalent cell lines were obtainable. Young states that the precise culture conditions are not set forth but offers no explanation of why such disclosure is necessary to duplicate either Gallo or Montagnier.

Paragraphs 18 and 19 speak to the confusion regarding the envelope protein of HIV at the time of the invention. The only point which Young makes which the examiner takes issue with is that in 19.b)i) and that only to the extent to which the point in time at which this fact became known is not established. If the last sentence of paragraph 19.a) is correct this would have been after the filing of the '501 application.

Paragraphs 20-24 are directed to a consideration of SN 06/659339. However, the extant rejection is based on the Chang et al. patent US 4,774,175.

YOUNG DECLARATION (ATTACHMENT B)

The Young Declaration (Attachment B under 37 C.F.R. § 1.132 filed

March 19, 1997 has been perused but as it is directed toward matters not under consideration in the instant case it has not been considered.

APPLICANT'S CITATION OF PRECEDENT AND THE SPECIFICATION IN RELATION TO THE *FORMAN* FACTORS

Applicant begins his response to the rejection made under 35 U.S.C. §112, first paragraph with citations of *Hybritech Inc. v. Monoclonal Antibodies*, *In re Chilowsky*, *In re Howarth* and *In re Wands* as precedent for what constitutes an enabling disclosure. In response the Examiner cites *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001-1007 (Fed. Cir. 1997):

> [2] It is true, as Genentech argues, that a specification need not disclose what is well known in the art. *See, e.g. Hybritech Inc. v. Monoclonal Antibodies Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed.Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

The examiner further notes that applicant's citation from *Wands* is superficial and actually originates in *In re Jackson*, 217 USPQ. The court's citation of *Jackson* is reproduced below:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. Ansul Co. v. Uniroyal, Inc. [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 [172 USPQ 257] (1972)]. the test

> is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed * * *.

The *Wands* court then referred to *Ex parte Forman* as follows:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

With regard to enablement the Court of Customs and Patent Appeals stated in *In re Cavallito and Gray*, 127 USPQ 203, (CCPA 1960):

> The mere statement of an inventive concept, however, is not a sufficient basis for claiming it. Sufficient information must be given to enable those skilled in the art to practice the invention.

nature of the invention

The invention is synthetic peptides from the *env* of HIV and their use in immunoassays for the detection of antibodies in patient sera.

the breadth of the claims

The claims embrace every synthetic peptide which can be produced from the putative *env* ORF and which is reactive with antibodies present in sera from individuals infected with HIV. The actual number of peptide species is not *a priori* determinable. One could calculate a potential number by determining the total number of hexamers, heptamers and on up to 40-mers which could be made, a crude estimate is 48,000. However, one cannot predict which peptides will specifically react with antibodies nor can one predict the influence of

additional peptides on a smaller peptide which binds antibodies. This issue has been considered in part in the discussion *supra* of the Hopp teachings.

predictability or unpredictability of the art

At the time the '501 and '534 application were filed there were no immunoassays which employed *env* polypeptides. Indeed, the actual revelation that the *env* ORF encoded the gp160 precursor which gives rise to gp120 and gp41 was not demonstrated until Essex (US 4,725,669). Applicant may argue that they correctly predicted the *env* ORF, however, this is not a demonstration of what actually is produced. Nor, at the time of filing of the '501 and '534 applications were immunoassays employing synthetic peptides from the *env* of HIV or any related, even if remote, human T cell lymphotrophic virus known.

In the absence of any evidence one cannot make any predictions.

relative skill of those in the art

It is clear from the Young Declaration, despite the examiner's criticisms of it, that the level of skill in the art was high.

state of the prior art

As noted above there were no immunoassays relying on *env* polypeptides, fragments thereof or synthetic peptides obtained therefrom. It is true, that p41 had been observed and postulated to be the *env* protein. It is also correct that this finding was somewhat off the mark in that p41 corresponds to the transmembrane portion of the viral envelope polypeptides and not to the surface envelope polypeptide which is gp120. It is also clear that certain research groups made inaccurate hypotheses regarding *env* even when in possession of the coding sequences. This reflects somewhat on the level of skill in the art since had these workers determined the amino acid sequence of p41 and compared it with the open reading frames of HIV it is difficult to see how they

could have made their hypotheses.

The Weiss declaration (submitted as reference C89) offers a striking picture of the state of the art in October, 1984. Dr Weiss carefully sets forth a record of the state of the art of retroviruses, particularly HTLV-I/II and what was know at the time about HIV. Dr. Weiss speaks to the confusion in the field of HIV in October of 1984. The laboratory of Gallo et al. was pursuing purported sequence similarities between HTLV-II and HTLV-III, and assumed that the structure of HTLV-III was similar to HTLV-II, leading them to misidentify the size and location of the *env* protein(s). Weiss states that until November, 1984, no-one knew that the envelope was encoded by the long *env* reading frame, and there was no basis for knowledge of the processing of the large *env* proteins into two smaller proteins.

With respect to synthetic peptides as antigens for immunoassays of animals immune responses see the discussion *supra* concerning Leach (1983).

In short, the art was in flux.

Applicant may argue that he has calmed things down by providing the sequence of HIV and its open reading frames, especially *env*. However, the presence of an open reading frame in and of itself does not mean that the actual proteins encoded thereby has been demonstrated. Indeed, there is no description of the actual proteins made in either the '501 or '534 specifications. Certain aspects of this problem are discussed below with respect to the Peterlin Declaration.

quantity of experimentation necessary

There is no way to predict how much experimentation is required to obtain a synthetic peptide which will permit the detection of anti-*env* antibodies in patient sera.

presence or absence of working examples

The specification has no working examples of synthetic peptides nor of synthetic peptides employed in immunoassays. The only example relating to *env* concerns recombinant expression of a polypeptide from a vector whose insert contains the *env* region as well as additional 5' and 3' sequences. The product of this expression vector was detected by immunofluorescence. The actual proteins synthesized by the vector were not determined. No description as to how to determine what the actual *env* gene products made is set forth in the '501 and '534 specifications. The *env* ORF is not the sole translatable sequence present in the expression vector nor could it have been predicted that transcription of the vector would have been unaccompanied by splicing of the mRNA. Applicant has previously submitted the Peterlin Declaration (Paper No. 16, October 2, 1995)) wherein it is asserted that the experiments of Rekosh et al. (1988), Bird et al. (1990) and Kimura et al. (1994) confirm the findings of the '501 specification. They do not do so because they do not duplicate the experiment of the '501 specification. Indeed, the last paragraph of Rekosh et al. provides interesting comment in this regard.

> The expression of gp160 from pSVSX1 presents an interesting enigma because the protein is encoded in the third coding region downstream from the SV40 late promoter. Either gp160 is efficiently translated from a polycistronic mRNA, a situation not often found in eukaryotic cells, or the regions including the first exons of *tat* and *art/trs* are spliced out of the mRNA used to make gp160. However, no splice acceptor site has yet been identified in the region between *tat*, *art/tas*, and *env*, that would enable such a splice to occur.

amount of direction or guidance presented

The specification does not provide guidance with respect to synthetic peptides obtained from *env* for use in immunoassays.

Consideration of all the *Forman* factors warrants the conclusion that despite the high level of skill in the art applicant's specification fails to provide an enabling disclosure for the instantly claimed invention.

APPLICANT'S RESPONSE

In their response at page 5 applicant's assert that:

> The specification from the outset has specifically taught that the polyeptides of the invention, including "immunologically active fragments" may be used as diagnostic reagents and has provided a representative list of immunogenic assays in which they could be used.

However, what is at issue are synthetic peptides which one of skill in the art would not immediately envision as being represented by the term "immunologically active fragments." This is particularly true with respect to the instant specification wherein fragments are discussed in respect to expression products of the *gag* and *env* polypeptides. Nor does the specification speak to "immunogenic" assays. The assays which are described in the instant specification are assays for the detection of antibodies and are not detecting immunogenicity.

Footnote 4 at page 7 asserts that "While reference in the above passages at times to polypeptides expressed by *env* and *gag* genes, the description is also generic to "antigen" or "antigenic polypeptide," which the '501 specification teaches at page 3 can be made synthetically." This assertion is untenable as it requires taking the teaching at page 3 out of its context. As noted above in discussing the Young declaration there is no nexus between the vaccine teachings of the SUMMARY OF THE INVENTION and the passages describing immunoassays.

In responding to the Office Action applicant asserts that the teachings of the specification at page 3 are not in a vacuum. Applicant asserts that

> Having made the synthetic peptide one would be directly led by the specification to use that peptide in the very procedures taught by the specification-an immunoassay to detect antibodies to HIV and as a vaccine. That conclusion is inescapable.

Unfortunately, the conclusion escapes the examiner since there is no nexus between the ultimate phrase of the SUMMARY OF THE INVENTION and any discussion of immunoassays in the specification.

At page 8 applicant asserts that

> The specification specifically teaches that synthetic polypeptides can be used in the claimed immunoassays . . .

Applicant is encouraged to cite the pages and lines wherein any assay employing a synthetic peptide is set forth in the '501 specification, muchless one which fulfills the language of the instant claims.

At page 11 applicant states

> Both the Hopp publications and the present application, however, are directed to epitopes that are tested to ensure that they are identified by antibodies raised by infected humans. That very test ensures that the epitopes are, in fact, immunogenic.

This is scientifically incorrect. The mere fact that antibodies present in patient sera recognize synthetic peptides says nothing about whether or not the peptides are immunogenic. At best, such studies confirm that they are antigens.

With regard to applicant's argument that how one skilled in the art would have regarded the Geysen et al technique is not the test for enablement the examiner cannot agree. At the time of Geysen et al. there was considerable controversy concerning the relevance of peptide antigens, indeed one need look no further than Leach (1983), "How antigenic are antigenic peptides?" for a cogent discussion of the problems with synthetic peptides. If workers of skill regarded Geysen et al. or Hopp et al. with skepticism then there is every reason

to believe that said workers would expect an actual example.

Applicant's assertion in footnote 9 that "the '501 specification teaches that at least 15 amino acids (corresponding to 45 bp) preferably be used" is inaccurate in that the passage in which it occurs concerns recombinant expression of polypeptides.

Applicant's reference to the Chiron and Abott Laboratories, while interesting, cannot be relied upon for precedent since the decision is unpublished.

It is unclear what point applicant is making in his discussion of Popovic et al. since it is clear from Popovic and the Levy patent that prior to the filing of the '501 application that the art had solved the problem of obtaining cell lines which would produce HIV. In the same paragraph applicant asserts "the well-known variability of the virus," but offers no evidence.

Applicant concludes the Popovic et al. paragraph by stating that "no sequence for any isolate had been published by October 31, 1984." What point is applicant making? Is applicant asserting that sequencing an isolated strain is inventive? Is applicant asserting that sequencing an isolated strain requires undue experimentation?

Applicant asserts that the teachings of the Schupbach et al. reference could not be reproduced as the cell line involved was not available to the general public nor was it described in sufficient detail to permit its duplication. The Schupbach et al. paper makes reference to Popovic et al. and Sarngadharan et al. The Popovic et al. reference has been discussed above in the consideration of the Young declaration. Neither Young nor applicant has clearly set forth why one of skill in the art could not have duplicated the Popovic et al. cell line. Indeed, Levy appeared to have done so. Applicant concludes his

analysis with

> Indeed, the conclusion that HIV was a "true member" of the HTLV family with significant antibody cross-reactivity and sequence homology coming from an important research group was a red herring that actually led away from the discovery of the true HIV DNA and polypeptide sequences.

This is excellent hyperbole. Just how the Schupbach et al. results effect the RNA sequence of HIV is unclear. But it is true that the assumption that p41 was the sole envelope protein was in error.

Nonetheless, the results of Schupbach et al. clearly establish that p41 is a viral polypeptide which is recognized by antibodies in patient sera. Is it critical to making synthetic peptides from p41 that it be known that it is from *env*? Not really. What would be critical would be obtaining sufficient p41 to permit sequencing. Given cell lines which produce the virus and the level of skill in the art it would appear to be a matter of routine experimentation.

Claims 60-67 are again rejected under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Applicant asserts that his discussion of the preceding enablement rejection completely addresses the instant rejection. Unfortunately, applicant's arguments concern synthetic peptides recognized by antibodies and not immunogenic synthetic peptides.

NEW GROUNDS OF REJECTION

Claims 60-67 are rejected under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

Neither the instant specification nor any of its parents or grandparents contains a written description of the now claimed invention.

Disregarding the issue of immunogenic there is no description in the specification of any of the instantly recited assays nor the now recited polypeptide composition. The entire thrust of applicant's specification and examples is to recombinantly produced HIV polypeptides and fragments thereof. the sole example of an *env* based immunoassay in the '501 and '534 involves recombinant expression from an open reading frame vector containing *env* and approximately 400 bp of additional coding material 5' thereto. This is certainly not a description of an immunoassay or composition containing a synthetic peptide, assuming that synthetic peptide means a solid-phase produced peptide of less than 40 amino acids. Nowhere in the specification is there even passing reference to methods for synthesis of synthetic peptides despite references to art such as "[t]he well-established Southern technique (J Mol Biol (1975) 98:503)" at page 6 of the '501 specification.

PRIORITY DATE BASED REJECTIONS

Claims 60-67 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Chang et al. (US Patent 4,774,175). See for example claims 2-15.

Claims 60-67 are rejected under 35 U.S.C. § 102(b) as being anticipated by Cosand (US Patent 4,629,783). Cosand describes peptides from the env domain of HIV and their use in solid phase immunoassays for the detection of antibodies present in the sera of patients infected with HIV.

Claims 60-67 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Chang et al. (US Patent 4,774,175) for the reasons of record.

Claims 60-67 are rejected under 35 U.S.C. § 102(e) as being clearly anticipated by Cosand (US Patent 4,629,783) for the reasons of record.

These rejections will be maintained until such time as applicant

overcomes the extant rejections under 35 U.S.C. §112, first paragraph.

Claims 60-67 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"a synthetic polypeptide comprising an envelope antigen comprising an immunogenic amino acid sequence of the *env* domain of HIV, wherein said antigen is a synthetic polypeptide" and its variants are confusing.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 60-67 are rejected under 35 U.S.C. 103(a) as being

unpatentable over either the combined teachings of Schupbach et al., Sarngadharan et al. and Popovic et al. or in combination with Levy (US 4,716,102) and in view of the level of skill in the art as set forth in the Young Declaration.

Schupbach et al., Sarngadharan et al. and Popovic et al. establish that p41 is a major antigen of HIV virus, presumably the envelope antigen. The teachings of Popovic et al. would permit the isolation of sufficient quantities of virus to permit the sequencing of either or both p41 and the viral genome. From the Young declaration one can conclude that given sequence information regarding a protein either in the form of an amino acid sequence determined directly from the protein or deduced from its gene that one of ordinary skill in the art could routinely make synthetic peptides which would function in immunoassays for the presence of viral antigens. Since the dangers of working with an infectious virus are immediately apparent it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have produced synthetic peptides for use in immunoassays of anti-HIV antibodies.

If, indeed, Popovic is non-enabling for the production of cell lines capable of producing virus then the teachings of Levy are required. Levy deposited such HIV producing cell lines and therefore would enable the isolation of sufficient quantities of either p41 or its corresponding nucleic acid sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MP Woodward whose telephone number is (703) 308-3890. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the

examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

The fax phone number for this Art Unit is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800

May 25, 1997